IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Gladwin et al.
Application No. 10/563,683
Filed: January 6, 2006
Confirmation No. 3225
For: USE OF NITRITE SALTS FOR THE TREATMENT OF CARDIOVASCULAR CONDITIONS

SUBMITTED VIA EFS

Examiner: Anna Pagonakis
Art Unit: 1614
Attorney Reference No. 4239-67618-07

COMMISSIONER FOR PATENTS
SUBMITTED VIA ELECTRONIC FILING SYSTEM

DECLARATION OF DR. S. BRUCE KING UNDER 37 C.F.R. § 1.132

I, S. Bruce King, Ph.D., declare as follows:

1. I have no financial interest in the above referenced patent application and I am not a listed inventor of the invention disclosed in the above referenced patent application.

2. A copy of my *curriculum vitae* is attached hereto as **Exhibit A**. At present, I hold a position as professor in the Chemistry Department of Wake Forest University, Winston-Salem, North Carolina. I have had 20 years of experience in research, including work on the physiological effects of nitric oxide and inorganic nitrite and particularly the effects of these molecules on vascular tone. I have published over 70 scientific articles in scientific journals and books. By virtue of my education, training, and professional experience, I am knowledgeable about nitric oxide donors, the physiology and biology of vasodilatation, and the effects of various compounds on vasodilatation.

3. Sodium nitroprusside (SNP) and 3-morpholino-sydnonimine (SIN) are structurally different molecules that act as nitric oxide donors. Sodium nitroprusside is an iron-based metal complex while SIN is a heterocyclic organic compound. Sodium nitrite is a simple inorganic salt and is structurally distinct from SNP and SIN. These two nitric oxide donors are structurally

dissimilar from inorganic nitrite and form NO in different manners through distinct chemical mechanisms. SNP and SIN release NO directly whereas sodium nitrite is converted via reactions with heme groups to form NO *in* vivo. Prior to October 14, 2003, I did not believe that inorganic nitrites were equivalent substitutes for recognized spontaneous nitric oxide donors, such as SNP or SIN, under physiological conditions *in vitro* or *in vivo*. I believe that my understanding accurately reflects the conventional wisdom in the field.

4. I have read Zhang *et al. J. Cereb. Blood Flow Metab.*, 14:217-26, 1994 (attached hereto as **Exhibit B**) and familiarized myself with the teachings therein. This reference teaches that SNP and SIN increase blood flow and reduce brain damage in focal ischemia in experiments with rats. Prior to October 14, 2003, I would not have understood that inorganic nitrites could substitute for these nitric oxide donors to increase blood flow and reduce brain damage in focal ischemia. This belief is based on my understanding of the differences between inorganic nitrites and recognized nitric oxide donors (such as SNP and SIN).

5. All statements made herein and of my own knowledge are true and all statements made on information are believed to be true; and further, these statements were made with the knowledge that willful false statements and like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that any such willful false statements made may jeopardize the validity of the application or any patent issuing thereon.

Date 9/3/09

S. Bruce King, Ph.D.